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Regioselective ring-opening of epoxides with *ortho*-lithioanisoles catalyzed by $BF_3 \cdot OEt_2$

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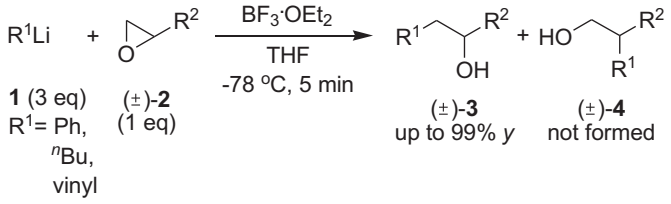
ABSTRACT

It is presented that a number of *o*-2-hydroxyalkylanisoles could be efficiently synthesized through the regioselective ring-opening reaction of epoxides with *o*-lithioanisoles in the presence of $BF_3 \cdot OEt_2$ Lewis-acid catalyst. Sterically demanding *o*-lithioanisoles had to be generated by exploiting the combination of ^{n}BuLi and a catalytic amount of TMEDA (0.20 equiv) in Et_2O as the lithiator whereas 'normal' anisole could be lithiated at *ortho*-position by treatment with ^{n}BuLi in THF as usual. Surprisingly, the availability of THF and a catalytic amount of TMEDA (0.20 equiv) in the reaction mixture was found to enhance the reaction yields dramatically. A complex aggregate formation by the co-operative ligation of THF and TMEDA to *ortho*-lithioanisole(s) was proposed to rationalize the high reactivity achieved in the ring-opening reaction of epoxides.

1. Introduction

Epoxides are among the most versatile intermediates in organic synthesis because they can be subjected to diverse stereoselective transformations for the synthesis of higly valuable products.[1] For example, the regio- and stereoselective ring-opening reaction of epoxides with carbon based nucleophiles is a well suited technique for the generation of new carbon–carbon bonds in a very simple and stereodefined manner.[2] Consequently, a number of catalytic methods for the ring-opening of epoxides with carbon nucleophiles ranging from cyanide[3,4] to organometallic compounds, such as Grignard reagents,[5] organocuprates,[6] organolithiums[7] as well as organoaluminums[8] have been developed in recent years.[9,10] Additionally, Friedel–Crafts type alkylation of electron-rich aromatic compounds with epoxides by using $SnCl_4$ as a Lewis-acid catalyst,[11] ring-opening of epoxides with indoles in 2,2,2-tifluoroethanol and in the presence of certain Lewis-acids[12] as well as ring-opening of epoxides with boron esters of electron-rich phenols as carbon nucleophiles[13] were also reported as C–C bond forming reactions.[14]

Organolithium compounds are one of the most useful nucleophiles in organic synthesis regarding their easy availability as well as their well established reactivity.[15] Organolithiums can act as nucleophiles or bases depending on their nature, the structure of epoxide ring as well as experimental conditions.[16] In 1984, Ganem and co-workers showed that the epoxide ring can be efficiently opened with simple organolithiums bearing no functional group by using $BF_3 \cdot OEt_2$ as the Lewis-acid catalyst (Scheme 1).[7a] Only one ((±)-3) of the possible regioisomers was obtained in high yields as



Scheme 1. $BF_3 \cdot OEt_2$ catalyzed epoxide opening with organolithium compounds.[7a]

the sole product formed through the fully regioselective attack of organolithium to the less substituted carbon atom of the epoxide ring. Inspired by the contribution from Ganem and co-workers and considering the easy preparation of *o*-metalated anisoles as well, we reasoned that *ortho*-lithioanisoles could be suitable nucleophiles for the regioselective ring-opening of epoxides. Herein, we are presenting that a variety of epoxides can be regioselectively opened with a number of *o*-lithioanisole nucleophiles in the presence of $BF_3 \cdot OEt_2$ catalyst.

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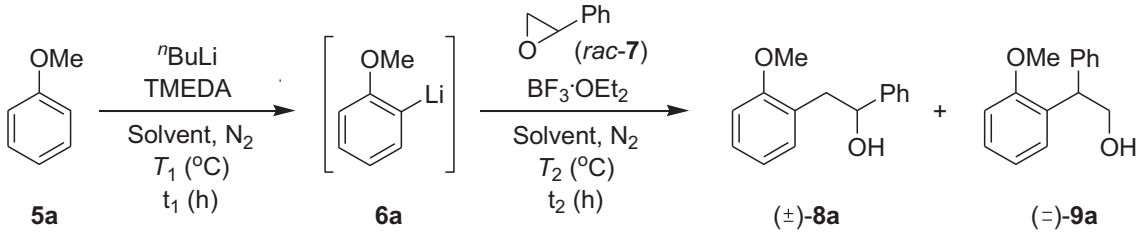
2. Results and discussion

The chemo- and regioselective metalation of aromatic substrates and treatment of the intermediate organometallics with electrophiles is a powerful methodology for introducing new functionalities to an aromatic ring.[17] In particular, the directed *ortho*-lithiation of aromatic compounds bearing a directing metalation group (DMG) is a widely used synthetic approach in this sense.[18,19]

Our approach toward the ring-opening of epoxides with *o*-lithioanisoles was simply designed as a one-pot two-step procedure: in the first step, an anisole could be lithiated at the *ortho*-position as usual and in the second step, the generated *o*-lithioanisole would be allowed to react with an epoxide in the presence of $BF_3{\cdot}OEt_2$ at −78 °C for 1 h. Racemic styrene oxide (*rac*-**7**) was first subjected to the ring-opening with *o*-lithioanisole (**6a**) (Table 1). When *o*-lithioanisole (**6a**) that was generated by employing equimolar amounts of anisole (**5a**) and ^{n}BuLi in THF was treated with *rac*-**7** in the presence of $BF_3{\cdot}OEt_2$ at −78 °C for 1 h the ring-opened products *rac*-**8a** and *rac*-**9a** were obtained in good yield (75%) with good regioselectivity (*rac*-**8a**/*rac*-**9a**=88:12, entry 1). This result was evaluated unsatisfactory in terms of the reaction yield and regioselectivity by us, in view of the results on the ring-opening of *rac*-**7** with phenyllithium in the presence of $BF_3{\cdot}OEt_2$ that were achieved by Ganem and co-workers (84% yield, >99% regioselectivity, Scheme 1).[7a] On the other hand, *o*-lithiation by using equimolar amounts of ^{n}BuLi and TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) in THF and treating the resulting *o*-lithioanisole (**6a**) with *rac*-**7** in the presence of $BF_3{\cdot}OEt_2$ did not lead to formation of the desired products (entry 2). Employment of equimolar amounts of ^{n}BuLi and TMEDA as the lithiation mediator in Et_2O instead of THF did not afford the desired products *rac*-**8a** and *rac*-**9a**, even in the presence of up-to 6.00 equiv of $BF_3{\cdot}OEt_2$ (entries 3–5). At this point, we concluded that TMEDA inhibits the nucleophilicity of *o*-lithioanisole(s) toward epoxide ring and adequately reasoned that the TMEDA-free aryllithium compound is necessary for the high yielding ring-opening reaction of epoxide. Additionally, Slocum and co-workers had shown that lithiation of anisole (**5a**) with ^{n}BuLi in the presence of catalytic TMEDA (20 mol %) in Et_2O at prolonged reaction times proceeds as efficiently as in the presence of equimolar amount of TMEDA.[20] Thus, we considered that the generation of *o*-lithioanisole (**6a**) by lithiation with ^{n}BuLi and catalytic TMEDA[20] in Et_2O and its subsequent treatment with *rac*-**7** in the presence of $BF_3{\cdot}OEt_2$ could be a suitable procedure for the ring-opening of the epoxide *rac*-**7**. This approach was then proven to be successful so that the ring-opened products *rac*-**8a** and *rac*-**9a** were obtained in 42% overall yield by employing ^{n}BuLi and catalytic TMEDA as the lithiator (entry 6). Despite the fact that simple anisoles can be lithiated at *ortho*-position with ^{n}BuLi in THF without the extra necessity for TMEDA, we prepared *o*-lithioanisole by lithiating anisole with the equimolar amount of ^{n}BuLi and catalytic TMEDA (20 mol % compared to anisole) in THF and the resulting *o*-lithioanisole was subjected to the $BF_3{\cdot}OEt_2$ catalyzed ring-opening of styrene oxide. Delightfully, the ring-opening reaction took place in almost quantitative yield (97% total yield, *rac*-**8a**/*rac*-**9a**=85:15, entry 7). Decrease in the amount of *o*-lithioanisole (**6a**, from 3.00 to 2.50 equiv) and TMEDA (from 0.60 to 0.30 equiv compared to anisole) resulted in lower yield (entries 7, 8, and 1).

Next, we turned our attention to studying the ring-opening of racemic styrene oxide (*rac*-**7**) with the sterically more demanding *o*-lithioanisoles **6b** and **6c** (Table 2). When lithiation of 2,4-di-*tert*-butylanisole (**5b**) was tried out at different temperatures in THF and subsequent addition of *rac*-**7** in the presence of $BF_3{\cdot}OEt_2$ was performed as described, almost no conversion of *rac*-**7** observed, even at prolonged lithiation times up to 16 h (Table 2, entries 1–3). This might be due to the fact that the deprotonation of THF with ^{n}BuLi is kinetically more favorable than the sterically hindered anisole **5b**.[21] On the other hand, the ring-opening products *rac*-**8b** and *rac*-**9b** were obtained in 52% total yield by employing Et_2O as the solvent

Table 1
Ring-opening of racemic styrene oxide (*rac*-**7**) with *o*-lithioanisole (**6a**) in the presence of $BF_3{\cdot}OEt_2$[a]

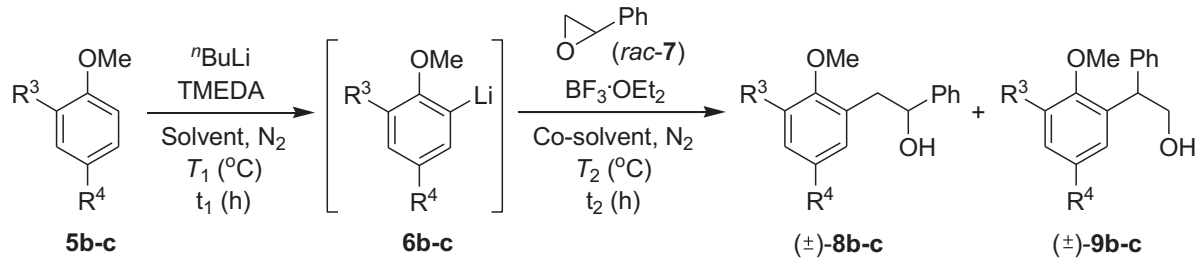


5a **6a** (±)-**8a** (±)-**9a**

Entry	**5a** and ^{n}BuLi (equiv)	TMEDA (equiv)	Solvent	T_1 (°C) t_1 (h)	$BF_3{\cdot}OEt_2$ (equiv)	T_2 (°C) t_2 (h)	Yield[b] (%)	Regioisomeric ratio ((±)-**8a**/(±)-**9a**)[c]
1	3.00	—	THF	0→rt 3	2.50	−78 1	75	88:12
2	3.00	3.00	THF	0→rt 3	2.50	−78 1	—[d]	
3	3.00	3.00	Et_2O	0→rt 3	2.50	−78 1	—[d]	
4	3.00	3.00	Et_2O	0→rt 3	4.50	−78 1	—[d]	
5	3.00	3.00	Et_2O	0→rt 3	6.00	−78 1	<10	n.d.
6	3.00	0.60	Et_2O	0→rt 3	2.50	−78 1	42	87:13
7	3.00	0.60	THF	0→rt 3	2.50	−78 1	97	85:15
8	2.50	0.30	THF	0→rt 3	2.50	−78 1	85	86:14

[a] The reactions were carried out by employing 1.0 mmol (1.00 equiv) *rac*-**7** and 8 mL of solvent.
[b] Isolated yields.
[c] Determined by the integration of the ^{1}H NMR spectra of the crude product.
[d] No conversion of *rac*-**7** was observed.

Table 2
Ring-opening of racemic styrene oxide (*rac*-**7**) with the sterically demanding *o*-lithioanisole **6b**–**c** in the presence of $BF_3{\cdot}OEt_2$[a]



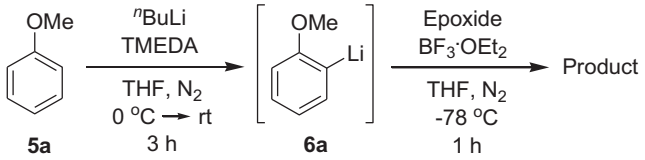
Entry	Anisole ^{n}BuLi (equiv)	TMEDA (equiv)	Solvent (Co-solvent)	T_1 (°C) t_1 (h)	$BF_3{\cdot}OEt_2$ (equiv)	T_2 (°C) t_2 (h)	Yield[b] (%)	Regioisomeric ratio ((±)-**8b**–**c**/(±)-**9b**–**c**)[c]
1	**5b** 3.00	0.60	THF (—)	0→rt 3→16	2.50	−78 1	—[d]	—
2	**5b** 3.00	—	THF (—)	0→rt 3→16	2.50	−78 1	—[d]	—
3	**5b** 3.00	0.60	THF (—)	−78→0 5	2.50	−78 1	—[d]	—
4	**5b** 3.00	0.60	Et_2O (—)	0→rt 16	2.50	−78 1	52	91 : 9
5	**5b** 3.00	0.60	*c*-Hexane (THF)	0→rt 16	2.50	−78 1	<10	90:10
6	**5b** 4.00	0.80	Et_2O (THF)	0→rt 16	3.30	−78 1	58	86:14
7	**5b** 5.00	1.00	Et_2O (THF)	0→rt 16	4.20	−78 1	77	86:14
8	**5c** 5.00	1.00	Et_2O (—)	0→rt 16	4.20	−78 1	46	83:17
9	**5c** 5.00	1.00	Et_2O (THF)	0→rt 16	4.20	−78 1	79	86:14
10	**5c** 5.00	1.00	THF (—)	0→rt 16	4.20	−78 1	<10	n.d.

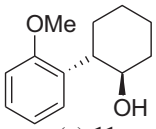
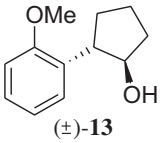
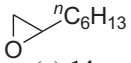
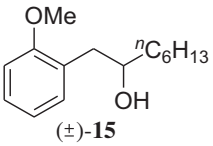
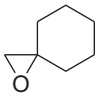
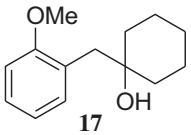
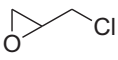
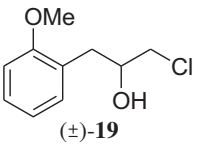
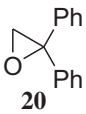
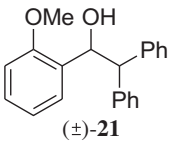
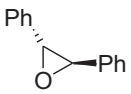
[a] The reactions were carried out by employing 1.0 mmol (1.00 equiv) *rac*-**7** and 8 mL of solvent and 2 mL of co-solvent.
[b] Isolated yields.
[c] Determined by the integration of the ^{1}H NMR spectra of the crude product.
[d] No conversion of *rac*-**7** was observed.

instead of THF and in the presence of catalytic TMEDA (*rac*-**8b**/*rac*-**9b**=91:9, entry 4). Using *c*-hexane as the solvent led to the formation of the regioisomers *rac*-**8b** and *rac*-**9b** in lower yield (<%10, entry 5). By adding THF as the 'co-solvent' to the reaction mixture in Et_2O, the yield could be dramatically increased and the desired regioisomers *rac*-**8b** and *rac*-**9b** could be isolated in 77% yield starting from 5.00 equiv of 2,4-di-*tert*-butylanisole (*rac*-**8b**/*rac*-**9b**=86:14, entry 7). The suitability of our method was also examined for the regioselective ring-opening of *rac*-**7** with 6-phenyl-2-lithioanisole (**6c**) as another sterically demanding *o*-lithioanisole compound that was formed from 2-phenylanisole (**5c**) through lithiation with ^{n}BuLi and catalytic TMEDA in Et_2O and the *o*-2-hydroxyalkylanisoles *rac*-**8c** and *rac*-**9c** could be obtained in high yields via incorporation of THF as the co-solvent (entries 8 and 9). It is noteworthy that lithiation of 2-phenylanisole (**5c**) with ^{n}BuLi in THF at different temperatures in the presence or in the absence of catalytic TMEDA and subsequent addition of *rac*-**7** and $BF_3{\cdot}OEt_2$ to the reaction mixture at −78 °C did not result in conversion of *rac*-**7** (entry 10). The preferential reaction of ^{n}BuLi as a base with THF instead of 2-phenylanisole (**5c**) can account for this unsuccessful attempt, as in the case of 2,4-di-*tert*-butylanisole (**5b**, entries 1–3).

To find out the substrate scope of the ring-opening procedure of epoxides with *o*-lithioanisole (**6a**) further, we employed a number of representative epoxides (Table 3). Cyclohexene oxide (**10**) and cyclopentene oxide (**12**) gave the corresponding *o*-2-hydroxyalkylanisoles *rac*-**11** and *rac*-**13** nearly in quantitative yields, respectively (entries 1 and 2). It should be noted that the ring-opening of cyclohexene oxide (**10**) and cyclopentene oxide (**12**) with *o*-lithioanisole (**6a**) that was generated by lithiation of anisole (**5a**) with ^{n}BuLi and stoichiometric amount of TMEDA in Et_2O proceeded in high yields as well. The high reactivity of the bicyclic symmetrical epoxides **10** and **12** in the ring-opening with *o*-lithioanisole can be attributed to their high ring-strain. Vrancken and co-workers reported similar behavior of bicyclic symmetrical epoxides toward organolithium compounds in which the presence of the stoichiometric amounts of TMEDA or (−)-sparteine with regard to organolithiums did not hamper the $BF_3{\cdot}OEt_2$ catalyzed ring-opening of cyclohexene oxide (**10**) and cyclopentene oxide (**12**).[10d] 1,2-Epoxyoctane (*rac*-**14**), methylenecyclohexane oxide (**16**), and epichlorohydrin (*rac*-**18**) could be opened in moderate to good yields with *o*-lithioanisole (**6a**) under the standard reaction conditions, by employing the combination of catalytic TMEDA (0.60 equiv)/^{n}BuLi (3.00 equiv)/anisole (3.00 equiv)/$BF_3{\cdot}OEt_2$ (2.50 equiv) in THF and by stirring at −78 °C for 1 h (entries 3–5). Careful analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy as well as GC–MS revealed no formation of the other possible regioisomers from the ring-opening of the terminal epoxides *rac*-**14**, **16** and *rac*-**18** with *o*-lithioanisole. It should be further noted that no conversion of the terminal epoxides *rac*-**14**, **16** and *rac*-**18** was observed when we used the stoichiometric amount of TMEDA in Et_2O

Table 3
Ring-opening of epoxides with *o*-lithioanisole (**6a**) in the presence of $BF_3 \cdot OEt_2$ as the Lewis-acid catalyst[a]

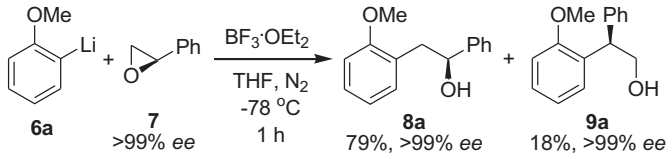


Entry	Epoxide	Product	Yield[b] (%)
1	 **10**	 (±)-**11**	99
2	 **12**	 (±)-**13**	99
3	 (±)-**14**	 (±)-**15**	77
4	 **16**	 **17**	75
5	 (±)-**18**	 (±)-**19**	53
6	 **20**	—	—[c]
7[d]	**20**	 (±)-**21**	45
8	 (±)-**22**	—	—[c]
9[d]	(±)-**22**	(±)-**21**	35

[a] The reactions were carried out by employing 3.00 mmol of anisole (**5a**), 3.00 mmol of ^{n}BuLi, 0.60 mmol of TMEDA, 1.0 mmol of epoxide, and 2.50 mmol of $BF_3 \cdot OEt_2$ in 8 mL THF.
[b] Isolated yields.
[c] No conversion of epoxide was observed.
[d] Epoxide was treated with *o*-lithioanisole (**6a**) at −78 °C in the presence of $BF_3 \cdot OEt_2$ and the reaction temperature was allowed to reach to 0 °C.

instead of catalytic TMEDA in THF. However, treatment of 2,2-diphenyloxirane (**20**) with *o*-lithioanisole (**6b**) at −78 °C for 1 h or for prolonged reaction times in the presence of $BF_3 \cdot OEt_2$ in THF neither gave any expected product nor conversion of the epoxide **20** (entry 6). Therefore, the epoxide **20** was then allowed to react with *o*-lithioanisole between −78 °C and 0 °C. However, we isolated the *o*-2-hydroxyalkylanisole *rac*-**21** as the sole reaction product, which can form via $BF_3 \cdot OEt_2$ catalyzed rearrangement of **20** to 2,2-diphenylacetaldehyde (hydride-migration, ~H) and the subsequent addition of *o*-lithioanisole (**6a**) to 2,2-diphenylacetaldehyde instead of the expected nucleophilic addition of *o*-lithioanisole (**6a**) to 2,2-diphenyloxirane (entry 7). Also *trans*-stilbene oxide (*rac*-**22**) was found to be sluggish in the $BF_3 \cdot OEt_2$ catalyzed nucleophilic addition of *o*-lithioanisole (**6a**) at −78 °C (entry 8). By allowing to react *trans*-stilbene oxide (*rac*-**22**) with *o*-lithioanisole (**6a**) in the presence of $BF_3 \cdot OEt_2$ at elevated temperature up to 0 °C, the *o*-2-hydroxyalkylanisole *rac*-**21** was obtained as the sole product through $BF_3 \cdot OEt_2$ catalyzed epoxide rearrangement (phenyl-migration, ~Ph) and the subsequent addition of *o*-lithioanisole (**6a**) to the corresponding carbonyl compound, 2,2,-diphenylacetaldehyde (entry 9). 1-Phenyl-1,2-epoxycyclohexane and *trans*-β-methylstyrene oxide as unsymmetrical epoxides could not give any ring-opened products with *o*-lithioanisole (**6a**) at −78 °C. We additionally attempted the ring-opening reaction of *trans*-stilbene oxide (*rac*-**22**) with phenyllithium (PhLi) instead of *o*-lithioanisole (**6a**) in the presence of $BF_3 \cdot OEt_2$ at −78 °C for 1 h, but no conversion of *trans*-stilbene oxide was detected by GC–MS. Based on all these observations, it can be concluded that the ring-opening reactivity of epoxides with aryllithiums catalyzed by $BF_3 \cdot OEt_2$ is significantly affected by the substitution patterns around epoxide ring.

The $BF_3 \cdot OEt_2$ catalyzed stereospecific ring-opening of epoxides with *o*-lithioanisoles was tested by reacting enantiomerically pure (*R*)-(+)-styrene oxide (**7**, >99% ee) with *o*-lithioanisole (**6b**) that was generated by lithiation of anisole (**5a**) as described above (Scheme 2). We are pleased to report that the corresponding *o*-2-hydroxyalkylanisoles **8a** and **9a** were obtained in enantiopure form with high yields and under high regioselectivity. The absolute configuration of **8a** ((*R*)-(−)-2-methoxyphenyl-1-phenylethanol) was determined by comparison of its sign of optical rotation with *ent*-**8a**, a known compound in the literature (see, Experimental section). Given the ready availability of enantiopure epoxides from racemic epoxides by the hydrolytic kinetic resolution,[22] this technique could be rather useful for the synthesis of enantiopure *o*-2-hydroxyalkylanisoles. This result also indicates that the $BF_3 \cdot OEt_2$ catalyzed ring-opening of epoxides with *o*-lithioanisoles is an S_N2-type process.



Scheme 2. $BF_3 \cdot OEt_2$ catalyzed stereospecific ring-opening of (*R*)-(+)-styrene oxide (**7**) with *o*-lithioanisole (**6a**).

Aggregation properties of any organolithium compound markedly vary in its solid-state, in solution, and in the gas phase.[18d,23] Additionally, the degree of aggregation as well as the distribution of aggregates in solution are strongly dependent on temperature, concentration as well as the presence of donor ligands. On the other hand, aggregation properties of organolithiums have decisive effects on the reaction yields and selectivities. However, it is often not easy to find out the reactivity of any organolithium compound because hetero-aggregates, besides homo-aggregates, can arise during the course of a reaction and this can add another complexity to rationalize a reaction mechanism.[23i,24] As for our catalytic system, the effect of lithiation yield of anisole on the conversion of styrene oxide (*rac*-**7**) can be ruled out since all the *ortho*-directed lithiation procedures employed are well established and recognized techniques

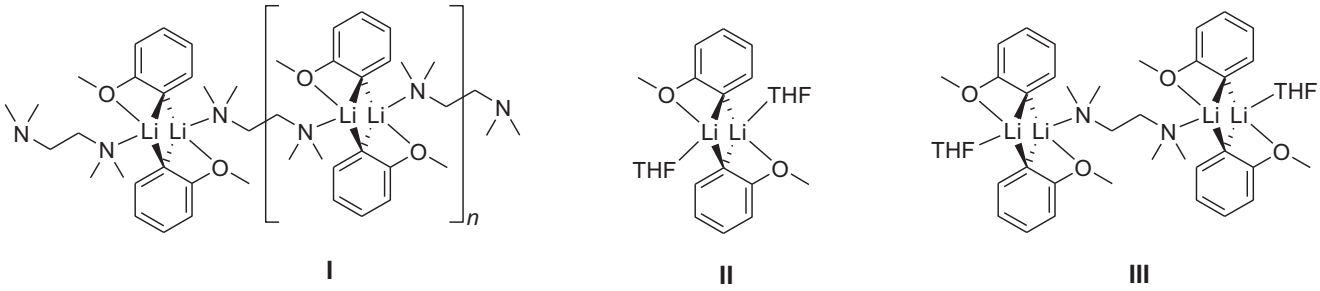


Fig. 1. Proposed aggregation types of *o*-lithioanisole (**6a**) in solution depending on the reaction conditions.

and should principally give similar lithiation yields. It was reported by Boersma and co-workers that *o*-lithioanisole (ArLi, **6a**) with 1.00 equiv TMEDA in Et_2O solution forms a $[(ArLi)_2\cdot(TMEDA)]$ type polymeric aggregate structure (**I**, Fig. 1).[25,23c] This type highly ordered polymeric aggregate structure can account for the inefficiency of *o*-lithioanisole in the ring-opening of *rac*-**7** (Table 1, entry 3). On the other hand, *o*-lithioanisole with 0.20 equiv TMEDA in Et_2O solution can form diverse aggregates, however, we are expecting formation of $(ArLi)_4$ type tetrameric aggregate besides the polymeric aggregate **I**. Thus, the ring-opening of *rac*-**7** could take place in mediocre yield (42%, Table 1, entry 6). Based on NMR studies in solution, Boersma and co-workers also suggested that *o*-lithioanisole in pure THF is arranged as $[(ArLi)_2\cdot(THF)_2]$ type dimeric aggregate (**II**, Fig. 1).[25] So, the higher reactivity of the dimeric aggregate II in the ring-opening of *rac*-**7** can be attributed to the formation lower aggregate structure (Table 1, entry 1).[18d] It was really curious that no ring-opening took place when *o*-lithioanisole was formed by employing equimolar amounts of ^{n}BuLi and TMEDA in THF, even in the presence of excessive $BF_3\cdot OEt_2$, up to 6.00 equiv (Table 1, entry 2). It has been often observed that THF is the stronger donor ligand than TMEDA when organolithium compounds come into consideration.[18d] In *o*-lithioanisole case, however, TMEDA seems to be competitive with THF and *o*-lithioanisole should predominantly have the polymeric aggregate structure **I**. Furthermore, the highest reactivity of *o*-lithioanisole in the ring-opening of *rac*-**7** that was achieved in the presence of catalytic TMEDA (0.20 equiv) in THF (Table 1, entry 7) might be explained by the formation of the complex tetrameric aggregate **III** in which two dimeric *o*-lithioanisole-subunits are bridged by the competitive coordination of one TMEDA molecule and one THF molecule is coordinated to each of dimeric subunits, $[(ArLi)_4\cdot(TMEDA)\cdot(THF)_2]$ (Fig. 1). Because the complex aggregate **III** is co-operatively coordinated by TMEDA and THF, it should be less stable and more reactive than the homo dimeric aggregate **II**. Thus, this finding suggests one of the rare examples on the competitive ligation of organolithium compounds by TMEDA against THF and related reactivity enhancement thereof.[18d,23a,26] Additionally, Mulliken population analysis at PM3 level of theory for the aggregate **II** and **III** was performed. Based on the computed Mulliken population analysis in which the structure of the aggregate **III** was simplified (see, Supplementary data), the charge distribution of the aggregate **II** is more uniform than that of the aggregate **III**. By comparing the computed Mulliken atomic charges of Li and C_{ipso}, the ionic character of C–Li bond in the aggregate **III** was found to be lower than that of the aggregate **II**. The lower ionic character of Li–C_{ipso} bond in the aggregate **III** can account for reduced stability. These computational results also support observed higher reactivity of the aggregate **III** than that of the aggregate **II** in the ring-opening of epoxides.

3. Conclusion

In conclusion, we have investigated the regioselective ring-opening of epoxides with *ortho*-lithioanisoles in the presence of $BF_3\cdot OEt_2$ as the Lewis-acid catalyst. Two one-pot protocols for the preparation of *o*-2-hydroxyalkylanisoles in high yields and regioselectivities were described: (i) Generation of simple *o*-lithioanisole (**6a**) by *ortho*-directed lithiation of anisole (**5a**) with ^{n}BuLi and catalytic TMEDA (0.20 equiv compared to ^{n}BuLi) in THF and subsequent treatment of the resulting *o*-lithioanisole (**6a**) with an epoxide at −78 °C in the presence of $BF_3\cdot OEt_2$ Lewis-acid catalyst; (ii) lithiation of the sterically demanding anisoles such as **5b** and **5c** with ^{n}BuLi and catalytic TMEDA (0.20 equiv compared to ^{n}BuLi) in Et_2O and subsequent treatment of the resulting *o*-lithioanisole **6b** and **6c** with an epoxide at −78 °C in the presence of $BF_3\cdot OEt_2$ Lewis-acid catalyst and THF as a co-ligand. Thus, the lithiation technique, which was originally developed by Slocum and co-workers[20] and includes the use of ^{n}BuLi and catalytic TMEDA (20 mol % of ^{n}BuLi) in Et_2O, was properly exploited for the *ortho*-lithiation of the sterically demanding anisoles **5b** and **5c**. The presence of THF and the catalytic TMEDA (0.20 equiv compared to ^{n}BuLi) was definitely found to be beneficial in terms of the reaction yields. The synergistic combination of THF and catalytic TMEDA for achieving high yields could be attributed to the formation of the complex aggregate **III** that represents one of the rare examples of the competitive coordination of TMEDA to organolithium compounds in the presence of THF. Considering that *o*-2-hydroxyalkylanisoles are the protected forms of the parent *o*-2-hydroxyalkylphenols,[27] epoxide ring-opening protocol described herein can serve as an efficient method for the synthesis of *o*-2-hydroxyalkylphenols.

4. Experimental section

4.1. General remarks

All reactions were carried out under an inert atmosphere of dry nitrogen (N_2) using oven-dried glassware. All reagents and solvents were transferred using gas-tight syringe and cannula techniques under N_2. Tetrahydrofuran (THF), diethyl ether (Et_2O), and *c*-hexane was freshly distilled under N_2 from sodium/benzophenone immediately prior to use. TMEDA was distilled under N_2 from calcium hydride (CaH_2). ^{n}BuLi (1.6 M solution in hexane), $BF_3\cdot OEt_2$ as well as the epoxides *rac*-**7**, **7**, **10**, **12**, *rac*-**14**, *rac*-**18**, **20**, *rac*-**22** were purchased from commercial suppliers and used as received. Methylenecyclohexane oxide (**16**) was prepared by the Corey–Chaykovsky epoxidation of cyclohexanone with trimethylsulfoxonium iodide. Anisole (**5a**) was provided by commercial suppliers. 2,4-Di-*tert*-butylanisole (**5b**) and 2-phenylanisole (**5c**) were prepared by methylation of the corresponding phenols with dimethyl sulfate (Me_2SO_4) in the presence of potassium carbonate (K_2CO_3) as the base in acetone. Thin layer chromatography (TLC) was conducted on aluminum sheets that were pre-coated with silica gel *SIL G/UV*$_{254}$ from MN GmbH & Co., in which the spots were visualized in UV-light (λ=254 nm) and/or by staining with phosphomolybdic acid. Chromatographic separations were performed using silica gel (MN-silica gel 60, 230–400 mesh). All melting points were determined in open glass capillary tube by means of

a BÜCHI Melting Point B-540 apparatus. Infrared (FT-IR) spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H and ^{13}C NMR spectra were recorded on a 500 MHz NMR spectrometer. Chemical shifts δ are reported in parts per million (ppm) relative to the residual protons in the NMR solvent ($CHCl_3$: δ 7.26) and carbon resonance of the solvent ($CDCl_3$: δ 77.00). NMR peak multiplicities were given as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra were recorded on a gas chromatography with mass sensitive detector from Agilent Technologies 6890 N Network GC System (EI, 70 eV) using Standard Method (column: HP-5MSI, 30 m, 0.25 mm ID, 0.25 μm film tickness; inlet: 300 °C (split modus); det: 300 °C; He, 1 mL/min (constant flow modus); oven: 40 °C (5 min), 5 °C/min, 280 °C (5 min)). High resolution electrospray ionization mass spectra (HR-ESI-MS) were obtained with MeOH on a Bruker micrOTOF-Q. The specific rotations ([α]) were measured on an Optical Activity Ltd. AA-55 polarimeter using 2 mL cell with a 0.5 dm path length and the sample concentrations are given in g/100 mL unit.

4.2. 2-(2-Methoxyphenyl)-1-phenylethanol (*rac*-8a)[28] and 2-(2-methoxyphenyl)-2-phenylethanol (*rac*-9a)[11] (Table 1, entry 7, general procedure)

An oven-dried 25 mL Schlenk tube that was capped with a glass stopper and equipped with a magnetic stirring bar was evacuated under heating with a blow-drier for 15 min. After the tube was cooled down to room temperature, dry nitrogen was back-filled and the glass stopper was replaced with a rubber septum under positive pressure of nitrogen. Anisole (**5a**, 324 mg, 325 μL, 3.0 mmol, 3.00 equiv) and TMEDA (70 mg, 90 μL, 0.6 mmol, 0.60 equiv) were added with a syringe in the tube succeeded by the addition of absolute THF (8 mL) as the solvent. After the mixture was cooled in an ice-bath, 1.875 mL of 1.6 M solution of ^{n}BuLi in hexanes (3.0 mmol, 3.00 equiv ^{n}BuLi) were dropwise added to the mixture. The mixture was then stirred for 3 h while the temperature was allowed to rise to room temperature. After the reaction tube was cooled down to −78 °C in a dry-ice/*iso*-propanol bath, styrene oxide (*rac*-**7**, 120 mg, 115 μL, 1.0 mmol, 1.00 equiv) and $BF_3{\cdot}OEt_2$ (355 mg, 310 μL, 2.5 mmol, 2.50 equiv) were successively added to the reaction mixture. After stirring the reaction mixture at −78 °C for 1 h, reaction was quenched by addition of saturated $NaHCO_3$ solution (8 mL). After THF was removed by rotary evaporation under reduced pressure, the aqueous residue was extracted with Et_2O (3×30 mL). Combined organic layers were dried over Na_2SO_4. After all volatile components were removed by rotary evaporation in vacuo, the residue was purified by silica gel column chromatography eluting with hexanes/EtOAc (9:1). The *o*-2-hydroxyalkylanisole *rac*-**8a** (180 mg, 0.79 mmol, 79%) was first isolated as a colorless viscous oil, which gradually became a colorless solid by standing whereas the *o*-2-hydroxyalkylanisole *rac*-**9a** (40 mg, 0.18 mmol, 18%) was obtained as a colorless oily product. *rac*-**8a**: mp: 72–74 °C; R_f=0.16 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3354 (m), 3289 (m), 3064 (m), 2836 (m), 2057 (w), 1928 (w), 1798 (w), 1602 (m), 1587 (m), 1497 (s), 1466 (s), 1454 (s), 1245 (s), 1180 (m), 765 (m), 745 (s), 699 (s); ^1H NMR (500 MHz, $CDCl_3$): δ 2.53 (d, J=3.1 Hz, 1H, O*H*), 2.99 (dd, J=13.7, 8.8 Hz, 1H), 3.12 (dd, J=13.7, 3.9 Hz, 1H), 3.86 (s, 3H), 4.97 (m, 1H), 6.90 (m, 2H), 7.08 (dd, J=7.8, 1.6 Hz, 1H), 7.22–7.28 (m, 2H), 7.33–7.36 (m, 2H),7.38–7.40 (m, 2H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 40.9 (CH_2), 55.1 (CH_3), 73.9 (CH), 110.2 (CH), 120.4 (CH), 125.6 (CH), 126.4 (C), 127.0 (CH), 127.7 (CH), 128.0 (CH), 131.3 (CH), 144.4 (C), 157.3 (C); GC–MS: t_R=29.95 min (*rac*-**8a**), m/z (%)=210 ([M−18]$^+$, 14), 194 ([M−34]$^+$, 1), 178 (2), 165 (8), 152 (4), 139 (1), 112 (100), 107 (32), 91 (29), 77 (21); HRMS (ESI$^+$): calcd for $C_{15}H_{16}O_2Na$ ([M+Na]$^+$) 251.1048, found 251.1045. *rac*-**9a**: R_f=0.08 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3354 (m), 3289 (m), 3064 (m), 2836 (m), 2057 (w), 1928 (w), 1798 (w), 1602 (m), 1587 (m), 1497 (s), 1466 (s), 1454 (s), 1245 (s), 1180 (m),765 (m), 745 (s), 699 (s); ^1H NMR (500 MHz, $CDCl_3$): δ 3.79 (s, 3H), 4.15 (m, 2H), 4.67 (t, J=7.2 Hz, 1H), 6.87 (d, J=8.1 Hz, 1H), 6.92 (dt, J=7.5, 1.1 Hz, 1H), 7.18 (dd, J=7.6, 1.5 Hz, 1H), 7.20–7.23 (m, 2H), 7.30 (m, 4H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 46.4 (CH), 55.5 (CH_3), 65.4 (CH_2), 110.8 (CH), 120.6 (CH), 126.5 (CH), 127.8 (CH), 128.2 (CH), 128.5 (CH), 128.5 (CH), 129.7 (C), 141.4 (C), 157.3 (C); GC–MS: t_R=28.59 min (*rac*-**9a**), m/z (%)=228 ([M]$^+$, 5), 213 ([M−15]$^+$, 100), 195 ([M−33]$^+$, 26), 181 (6), 165 (27), 151 (32), 135 (57), 121 (7), 105 (32), 91 (19), 77 (23); HRMS (ESI$^+$): calcd for $C_{15}H_{16}O_2Na$ ([M+Na]$^+$) 251.1048, found 251.1056.

4.3. (*R*)-(−)-2-(2-Methoxyphenyl)-1-phenylethanol (8a)[28] and (*R*)-(+)-2-(2-methoxyphenyl)-2-phenylethanol (9a) (Scheme 2)

Compound **8a**: $[\alpha]_D^{20}$ −8.4 (*c* 0.5, CH_2Cl_2), HPLC: Chiralcel OD-H, *n*-hexane/^{i}PrOH (90:10), 1.0 mL/min, 44 bar, 254 nm (UV–vis), t_R=7.97 min (*ent*-**8a**), t_R=9.28 min (**8a**). **9a**: $[\alpha]_D^{20}$ +40.0 (*c* 0.3, CH_2Cl_2), HPLC: Chiralcel OD-H, *n*-hexane/^{i}PrOH (90:10), 1.0 mL/min, 44 bar, 254 nm (UV–vis), t_R=8.86 min (*ent*-**9a**), t_R=10.09 min (**9a**).

4.4. 2-(3,5-Di-*tert*-butyl-2-methoxyphenyl)-1-phenylethanol (*rac*-8b) and 2-(3,5-di-*tert*-butyl-2-methoxyphenyl)-2-phenylethanol (*rac*-9b) (Table 2, entry 7)

An oven-dried 25 mL Schlenk tube that was capped with a glass stopper and equipped with a magnetic stirring bar was evacuated under heating with a blow-drier for 15 min. After the tube was cooled down to room temperature, dry nitrogen was back-filled and the glass stopper was replaced with a rubber septum under positive pressure of nitrogen. 2,4-Di-*tert*-butylanisole (**5b**, 1.102 g, ca. 1.23 mL, 5.0 mmol, 5.00 equiv) and TMEDA (116 mg, 150 μL, 1.0 mmol, 1.00 equiv) were added with a syringe in the tube succeeded by the addition of absolute Et_2O (15 mL) as the solvent. After the mixture was cooled in an ice-bath, 3.125 mL of 1.6 M solution of ^{n}BuLi in hexanes (5.0 mmol, 5.00 equiv ^{n}BuLi) were dropwise added to the mixture. The mixture was then stirred overnight (ca. 16 h) while the temperature was allowed to rise to room temperature. After the reaction tube was cooled down to −78 °C in a dry-ice/*iso*-propanol bath, absolute THF (3 mL) was added. Styrene oxide (*rac*-**7**, 120 mg, 115 μL, 1.0 mmol, 1.00 equiv) and $BF_3{\cdot}OEt_2$ (710 mg, 620 μL, 5.0 mmol, 5.00 equiv) were successively added to the reaction mixture. After stirring the reaction mixture at −78 °C for 1 h, reaction was quenched by addition of saturated $NaHCO_3$ solution (8 mL). After the ethereal solvents were removed by rotary evaporation under reduced pressure, the aqueous residue was extracted with Et_2O (3×30 mL). Combined organic layers were dried over Na_2SO_4. After all volatile components were removed by rotary evaporation in vacuo, the residue was purified by silica gel column chromatography eluting with hexanes/EtOAc (9:1). Both the *o*-2-hydroxyalkylanisoles *rac*-**8b** (221 mg, 0.65 mmol, 65%) and *rac*-**9b** (41 mg, 0.12 mmol, 12%) were obtained as colorless solids. *rac*-**8b**: mp: 63–65 °C; R_f=0.15 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3307 (s), 2961 (s), 1601 (w), 1477 (s), 1454 (s), 1427 (m), 1389 (m), 1323 (w), 1271 (m), 1231 (s), 1203 (m), 1156 (w), 1116 (s), 1077 (w), 1034 (s), 1010 (s), 950 (m), 907 (w), 878 (m), 772 (w), 754 (m), 697 (s), 652 (w), 541 (w); ^1H NMR (500 MHz, $CDCl_3$): δ 1.23 (s, 9H), 1.41 (s, 9H), 2.97 (br d, J=3.0 Hz, 1H), 3.09 (br d, J=6.3 Hz, 2H), 3.83 (s, 3H), 4.98 (dt, J=6.5, 2.9 Hz, 1H), 6.89 (br d, J=2.5 Hz, 1H), 7.22–7.26 (m, 2H), 7.29–7.35 (m, 4H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 31.3 (CH_3), 31.4 (CH_3), 34.4 (C), 35.3 (C), 42.0 (CH_2), 61.7 (CH_3), 74.9 (CH), 123.1 (CH), 125.7 (CH), 126.8 (CH), 127.2 (CH), 128.2 (CH), 130.8 (C), 142.1 (C), 144.4 (C), 146.0 (C), 155.9 (C); GC–MS:

t_R=33.41 min (*rac*-**8b**), *m*/*z* (%)=322 ([M−18]$^+$, 14), 307 ([M−33]$^+$, 19), 234 (63), 219 (100), 203 (6), 177 (11), 163 (10), 105 (13); HRMS (ESI$^+$): calcd for $C_{23}H_{32}O_2Na$ ([M+Na]$^+$) 363.2300, found 363.2277. *rac*-**9b**: mp: 86–88 °C; R_f=0.09 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3307 (s), 2961 (s), 1601 (w), 1477 (s), 1454 (s), 1427 (m), 1389 (m), 1323 (w), 1271 (m), 1231 (s), 1203 (m), 1156 (w), 1116 (s), 1077 (w), 1034 (s), 1010 (s), 950 (m), 907 (w), 878 (m), 772 (w), 754 (m), 697 (s), 652 (w), 541 (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (s, 9H), 1.40 (s, 9H), 3.66 (s, 3H), 4.03–4.08 (m, 1H), 4.10–4.15 (m, 1H), 4.68 (t, *J*=7.4 Hz, 1H), 7.20–7.23 (m, 2H), 7.28–7.35 (m, 5H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 31.3 (CH_3), 31.5 (CH_3), 34.6 (C), 35.4 (C), 46.4 (CH), 62.8 (CH_3), 67.1 (CH_2), 123.1 (CH), 123.7 (CH), 126.6 (CH), 128.3 (CH), 128.6 (CH), 133.2 (C), 141.6 (C), 142.3 (C), 145.7 (C), 156.4 (C); GC–MS: t_R=33.05 min (*rac*-**9b**), *m*/*z* (%)=340 ([M]$^+$, 37), 325 ([M−15]$^+$, 13), ([M−30]$^+$, 40), 295 (30), 281 (14), 253 (41), 207 (100), 191 (11), 178 (8), 165 (9), 147 (3), 133 (11), 119 (4), 105 (30); HRMS (ESI$^+$): calcd for $C_{23}H_{32}O_2Na$ ([M+Na]$^+$) 363.2300, found 363.2298.

4.5. 2-(2-Methoxy-3-phenylphenyl)-1-phenylethanol (*rac*-8c) and 2-(2-methoxy-3-phenylphenyl)-2-phenylethanol (*rac*-9c) (Table 2, entry 9)

An oven-dried 25 mL Schlenk tube that was capped with a glass stopper and equipped with a magnetic stirring bar was evacuated under heating with a blow-drier for 15 min. After the tube was cooled down to room temperature, dry nitrogen was back-filled and the glass stopper was replaced with a rubber septum under positive pressure of nitrogen. 2-Phenylanisole (**5b**, 921 mg, ca. 985 μL, 5.0 mmol, 5.00 equiv) and TMEDA (116 mg, 150 μL, 1.0 mmol, 1.00 equiv) were added with a syringe in the tube succeeded by the addition of absolute Et_2O (15 mL) as the solvent. After the mixture was cooled in an ice-bath, 3.125 mL of 1.6 M solution of ^{n}BuLi in hexanes (5.0 mmol, 5.00 equiv ^{n}BuLi) were dropwise added to the mixture. The mixture was then stirred overnight (ca. 16 h) while the temperature was allowed to rise to room temperature. After the reaction tube was cooled down to −78 °C in a dry-ice/*iso*-propanol bath, absolute THF (3 mL) was added. Styrene oxide (*rac*-**7**, 120 mg, 115 μL, 1.0 mmol, 1.00 equiv) and $BF_3{\cdot}OEt_2$ (710 mg, 620 μL, 5.0 mmol, 5.00 equiv) were successively added to the reaction mixture. After stirring the reaction mixture at −78 °C for 1 h, reaction was quenched by addition of saturated $NaHCO_3$ solution (8 mL). After the ethereal solvents were removed by rotary evaporation under reduced pressure, the aqueous residue was extracted with Et_2O (3×30 mL). Combined organic layers were dried over Na_2SO_4. After all volatile components were removed by rotary evaporation in vacuo, the residue was purified by silica gel column chromatography eluting with hexanes/EtOAc (9:1). Both the *o*-2-hydroxyalkylanisoles *rac*-**8c** (190 mg, 0.63 mmol, 63%) and *rac*-**9c** (55 mg, 0.18 mmol, 18%) were isolated as colorless viscous oil by silica gel column chromatography eluting with hexanes/EtOAc (9:1). *rac*-**8c**: R_f=0.15 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3434 (s), 3060 (s), 3028 (s), 2934 (s), 2835 (m), 2337 (w), 1950 (w), 1883 (w), 1811 (w), 1759 (w), 1672 (w), 1602 (m), 1574 (w), 1547 (w), 1496 (s), 1442 (s), 1419 (s), 1329 (m), 1253 (s), 1219 (s), 1172 (s), 1093 (s), 1046 (s), 1007 (s), 914 (m), 844 (w), 794 (m), 759 (s), 700 (s), 629 (w), 598 (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.0 (m, 1H, O*H*), 3.03 (dd, *J*=13.7, 8.7 Hz, 1H), 3.11 (dd, *J*=13.7, 4.0 Hz, 1H), 3.33 (s, 3H), 4.99 (m, 1H), 7.06–7.11 (m, 2H), 7.18–7.26 (m, 2H), 7.33 (t, *J*=7.4 Hz, 3H), 7.38–7.42 (m, 4H), 7.58 (d, *J*=7.7 Hz, 2H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 41.2 (CH_2), 60.3 (CH_3), 74.8 (CH), 124.2 (CH), 125.7 (CH), 127.1 (CH), 127.3 (CH), 128.2 (CH), 128.3 (CH), 128.9 (CH), 130.0 (CH), 130.7 (CH), 131.7 (C), 134.8 (C), 138.6 (C), 144.4 (C), 155.9 (C); GC–MS: t_R=35.19 min (*rac*-**8c**), *m*/*z* (%)=286 ([M−18]$^+$, 11), 270 ([M−34]$^+$, 1), 253 (3), 239 (3), 228 (2), 209 (40), 198 (100), 183 (20), 165 (17), 152 (16), 128 (3), 107 (21), 79 (17); HRMS (ESI$^+$): calcd for $C_{21}H_{20}O_2Na$ ([M+Na]$^+$) 327.1361, found 327.1328. *rac*-**9c**: R_f=0.08 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3434 (s), 3060 (s), 3028 (s), 2934 (s), 2835 (m), 2337 (w), 1950 (w), 1883 (w), 1811 (w), 1759 (w), 1672 (w), 1602 (m), 1574 (w), 1547 (w), 1496 (s), 1442 (s), 1419 (s), 1329 (m), 1253 (s), 1219 (s), 1172 (s), 1093 (s), 1046 (s), 1007 (s), 914 (m), 844 (w), 794 (m), 759 (s), 700 (s), 629 (w), 598 (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.12 (s, 3H), 4.19 (m, 2H), 4.72 (t, *J*=7.2 Hz, 1H), 7.17 (m, 1H), 7.21–7.25 (m, 2H), 7.30–7.34 (m, 5H), 7.38–7.41 (m, 3H), 7.56 (m, 2H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 46.8 (CH), 60.5 (CH_3), 66.0 (CH_2), 124.2 (CH), 126.6 (CH), 127.1 (CH), 127.5 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.9 (CH), 129.9 (CH), 135.0 (C), 135.1 (C), 138.7 (C), 141.7 (C), 156.0 (C); GC–MS: t_R=35.27 min (*rac*-**9c**), *m*/*z* (%)=304 ([M]$^+$, 4), 286 ([M−18]$^+$, 4), 274 ([M−30]$^+$, 30), 257 (9), 239 (3), 227 (4), 207 (100), 191 (11), 177 (4), 165 (13), 133 (8), 115 (4), 103 (4), 91 (45), 73 (3); HRMS (ESI$^+$): calcd for $C_{21}H_{20}O_2Na$ ([M+Na]$^+$) 327.1361, found 327.1359.

4.6. *trans*-2-(2-Methoxyphenyl)-cyclohexanol (*rac*-11)[10d] (Table 3, entry 1)

Cyclohexene oxide (**10**, 98 mg, ca. 101 μL, 1.0 mmol, 1.00 equiv) was reacted with *o*-lithioanisole (**6a**, ca. 3.00 equiv) in the presence of $BF_3{\cdot}OEt_2$ according to the general procedure as described above. The *o*-2-hydroxyalkylanisole *rac*-**11** (204 mg, 0.99 mmol, 99%) was first isolated by silica gel column chromatography eluting with hexanes/EtOAc (9:1) as a colorless viscous oil, which gradually became a colorless solid by standing. Mp: 52–54 °C; R_f=0.11 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3372 (m), 3103 (w), 3073 (w), 3012 (w), 2919 (s), 2661 (w), 2008 (w), 1911 (w), 1876 (w), 1756 (w) 1599 (s), 1585 (s), 1492 (s), 1463 (s), 1438 (s), 1326 (m), 1290 (m), 1240 (s), 1191 (m), 1126 (m), 1090 (w), 1051 (s), 961 (m), 824 (w), 746 (s), 730 (s), 577 (w), 565 (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33–1.54 (m, 4H), 1.73–1.86 (m, 4H), 2.12–2.16 (m, 1H), 2.98–3.04 (m, 1H), 3.71–3.77 (m, 1H), 3.83 (s, 3H), 6.89 (dd, *J*=8.2, 1.0 Hz, 1H), 6.97 (dt, *J*=7.5, 1.0 Hz, 1H), 7.20 (m, 1H), 7.23 (m, 1H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 25.1 (CH_2), 26.1 (CH_2), 32.3 (CH_2), 35.1 (CH_2), 45.0 (CH), 55.4 (CH_3), 73.8 (CH), 110.7 (CH), 120.9 (CH), 127.2 (CH), 127.3 (CH), 131.5 (C), 157.6 (C); GC–MS: t_R=28.19 min (*rac*-**11**), *m*/*z* (%)=206 ([M]$^+$, 73), 188 ([M−18]$^+$, 7), 173 ([M−33]$^+$, 43), 147 (23), 134 (7), 121 (100), 107 (9), 91 (47), 77 (10); HRMS (ESI$^+$): calcd for $C_{13}H_{18}O_2Na$ ([M+Na]$^+$) 229.1204, found 229.1196.

4.7. *trans*-2-(2-Methoxyphenyl)-cyclopentanol (*rac*-13) (Table 3, entry 2)

Cyclopentene oxide (**12**, 84 mg, 87 μL, 1.0 mmol, 1.00 equiv) was reacted with *o*-lithioanisole (**6a**, ca. 3.00 equiv) in the presence of $BF_3{\cdot}OEt_2$ according to the general procedure as described above. The *o*-2-hydroxyalkylanisole *rac*-**13** (190 mg, 0.99 mmol, 99%) was obtained as a colorless viscous oil after silica gel column chromatography eluting with hexanes/EtOAc (9:1). R_f=0.09 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3391 (s), 3064 (m), 3029 (m), 2955 (s), 2872 (s), 2835 (s), 2050 (w), 1893 (w), 1775 (w), 1599 (s), 1585 (s), 1492 (s), 1463 (s), 1438 (s), 1326 (m), 1290 (m), 1240 (s), 1175 (m), 1029 (s), 984 (m), 752 (s), 573 (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.67–1.73 (m, 1H), 1.74–1.92 (m, 3H), 1.98–2.10 (m, 2H), 2.44 (br s, 1H), 3.27 (dd, *J*=15.5, 7.9 Hz, 1H), 3.83 (s, 3H), 4.17 (dd, *J*=12.3, 6.8 Hz, 1H), 6.88 (dd, *J*=8.4, 1.0 Hz, 1H), 6.93 (dt, *J*=7.5, 1.0 Hz, 1H), 7.17–7.21 (m, 2H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 22.8 (CH_2), 30.3 (CH_2), 34.3 (CH_2), 48.6 (CH), 55.4 (CH_3), 79.4 (CH), 110.4 (CH), 120.8 (CH), 126.9 (CH), 127.1 (CH), 131.5 (C), 157.5 (C); GC–MS: t_R=26.76 min (*rac*-**13**), *m*/*z* (%)=192 ([M]$^+$, 68), 174 ([M−18]$^+$, 11), 159 ([M−33]$^+$, 9), 148 (14), 135 (11), 121 (100), 105 (10), 91 (50), 77 (14); HRMS (ESI$^+$): calcd for $C_{12}H_{16}O_2Na$ ([M+Na]$^+$) 215.1048, found 215.1042.

4.8. 1-(2-Methoxyphenyl)-2-octanol (*rac*-15) (Table 3, entry 3)

1,2-Epoxyoctane (*rac*-**14**, 128 mg, 153 μL, 1.0 mmol, 1.00 equiv) was reacted with *o*-lithioanisole (**6a**, ca. 3.00 equiv) in the presence of $BF_3{\cdot}OEt_2$ according to the general procedure as described above. Only the regioisomer *rac*-**15** (182 mg, 0.77 mmol, 77%) was obtained as a colorless viscous oil after silica gel column chromatography eluting with hexanes/EtOAc (9:1). R_f=0.23 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3400 (s), 3065 (m), 3025 (m), 2999 (m), 2928 (s), 2856 (s), 2482 (w), 2057 (w), 1893 (w), 1782 (w), 1601 (s), 1587 (s), 1493 (s), 1464 (s), 1377 (s), 1290 (m), 1240 (s), 1177 (s), 1122 (s), 1052 (s), 1031 (s), 968 (w), 944 (w), 860 (w), 800 (w), 752 (s), 727 (m), 612 (w), 571 (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J=6.8 Hz, 3H), 1.29 (m, 7H), 1.48 (m, 3H), 2.14 (br s, 1H), 2.67 (dd, J=13.5, 8.2 Hz, 1H), 2.87 (dd, J=13.5, 3.8 Hz, 1H), 3.80 (s, 3H), 3.82 (br s, 1H), 6.85 (d, J=8.2 Hz, 1H), 6.90 (dt, J=7.4, 0.8 Hz, 1H), 7.13 (dd, J=7.3, 1.4 Hz, 1H), 7.20 (dt, J=7.6, 0.8 Hz, 1H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 37.1 (CH_2), 38.6 (CH_2), 55.2 (CH_3), 71.8 (CH), 110.3 (CH), 120.6 (CH), 127.2 (C), 127.6 (CH), 131.3 (CH), 157.5 (C); GC–MS: t_R=29.14 min (*rac*-**15**), m/z (%)=236 ($[M]^+$, 3), 218 ($[M-18]^+$, 2), 147 (4), 122 (100), 107 (12), 91 (18), 77 (5); HRMS (ESI^+): calcd for $C_{15}H_{24}O_2Na$ ($[M+Na]^+$) 259.1674, found 259.1664.

4.9. 1-(*o*-Methoxybenzyl)-1-cyclohexanol (17) (Table 3, entry 4)

Methylenecyclohexane oxide (**16**, 112 mg, ca. 115 μL, 1.0 mmol, 1.00 equiv) was reacted with *o*-lithioanisole (**6a**, ca. 3.00 equiv) in the presence of $BF_3{\cdot}OEt_2$ according to the general procedure as described above. Only the regioisomer **17** (165 mg, 0.75 mmol, 75%) was obtained as a colorless viscous oil after silica gel column chromatography eluting with hexanes/EtOAc (9:1). R_f=0.31 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3543 (m), 3064 (w), 3025 (w), 2999 (w), 2931 (s), 2856 (s), 2661 (w), 1911 (w), 2481 (w), 2055 (w), 1896 (w), 1785 (w), 1600 (m), 1586 (m), 1493 (s), 1463 (s), 1439 (s), 1395 (m), 1321 (m), 1291 (m), 1242 (s), 1175 (m), 1148 (m), 1111 (s), 1051 (s), 1028 (s), 978 (s), 875 (w), 826 (w), 753 (s), 712 (w), 630 (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24–1.30 (m, 1H), 1.38–1.44 (m, 2H), 1.46–1.55 (m, 5H), 1.57–1.64 (m, 2H), 2.66 (s, 1H), 2.83 (s, 2H), 3.82 (s, 3H), 6.88 (d, J=8.2 Hz, 1H), 6.90 (dt, J=7.4, 0.8 Hz, 1H), 7.12 (dd, J=7.4, 1.6 Hz, 1H), 7.21 (dt, J=8.2, 1.6 Hz, 1H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 22.3 (CH_2), 25.9 (CH_2), 37.8 (CH_2), 42.6 (CH_2), 55.2 (CH_3), 72.0 (C), 110.5 (CH), 120.6 (CH), 126.0 (C), 127.7 (CH), 132.5 (CH), 157.5 (C); GC–MS: t_R=28.41 min (**17**), m/z (%)=220 ($[M]^+$, 1), 202 ($[M-18]^+$, 23), 177 (2), 159 (4), 144 (3), 122 (100), 107 (10), 91 (36), 77 (8); HRMS (ESI^+): calcd for $C_{14}H_{20}O_2Na$ ($[M+Na]^+$) 243.1361, found 243.1365.

4.10. 1-Chloro-3-(2-methoxyphenyl)-1-propanol (*rac*-19) (Table 3, entry 5)

Epichlorohydrin (*rac*-**18**, 93 mg, 78 μL, 1.0 mmol, 1.00 equiv) was reacted with *o*-lithioanisole (**6a**, ca. 3.00 equiv) in the presence of $BF_3{\cdot}OEt_2$ according to the general procedure as described above. Only the regioisomer *rac*-**19** (106 mg, 0.53 mmol, 53%) was obtained as a colorless viscous oil after silica gel column chromatography eluting with hexanes/EtOAc (9:1). R_f=0.18 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3434 (m), 3065 (w), 3003 (m), 2955 (m), 2837 (m), 2485 (s), 2053 (w), 1901 (w), 1786 (w), 1600 (s), 1587 (m), 1494 (s), 1464 (s), 1438 (s), 1314 (m), 1289 (m), 1244 (s), 1177 (m), 1161 (m), 1114 (s), 1079 (m), 1051 (s), 1029 (s), 934 (w), 886 (w), 846 (w), 754 (s), 735 (m) 697 (w), 569 (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.68 (m, 1H), 2.93 (d, J=6.3 Hz, 2H), 3.50 (dd, J=11.1, 6.1 Hz, 1H), 3.57 (dd, J=11.2, 4.5 Hz, 1H), 3.83 (s, 3H), 4.07–4.13 (m, 1H), 6.88 (d, J=8.2 Hz, 1H), 6.92 (t, J=7.5 Hz, 1H), 7.18 (d, J=7.4 Hz, 1H), 7.24 (m, 1H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 35.4 (CH_2), 49.3 (CH_2), 55.3 (CH_3), 71.3 (CH), 110.4 (CH), 120.8 (CH), 125.4 (C), 128.2 (CH), 131.4 (CH), 157.4 (C); GC–MS: t_R=25.93 min (*rac*-**19**), m/z (%)=200 ($[M]^+$, 15), 202 ($[M-18]^+$, 1), 164 (20), 151 (9), 133 (4), 121 (100), 107 (9), 91 (95), 77 (15); HRMS (ESI^+): calcd for $C_{10}H_{13}ClO_2Na$ ($[M+Na]^+$) 223.0502, found 223.0510.

4.11. 1-(2-Methoxyphenyl)-2,2-diphenylethanol (*rac*-21) (Table 3, entry 7)

After *o*-lithioanisole (**6a**) was generated by following the general procedure, the reaction tube was cooled down to −78 °C in a dry-ice/*iso*-propanol bath. 2,2-Diphenyloxirane (**20**, 196 mg, 1.0 mmol, 1.00 equiv) and $BF_3{\cdot}OEt_2$ (355 mg, 310 μL, 2.5 mmol, 2.50 equiv) were successively added to the reaction mixture. After the reaction mixture was stirred at −78 °C for 1 h, the reaction temperature was allowed to rise slowly to 0 °C. The reaction was quenched by addition of saturated $NaHCO_3$ solution (8 mL) at this point. After the usual working-up of the aqueous mixture according to the general procedure as described above, the *o*-2-hydroxyalkylanisole *rac*-**21** (138 mg, 0.45 mmol, 45%) was obtained as a colorless viscous oil via column chromatographic purification. R_f=0.16 (silica gel; hexanes/EtOAc, 9:1); FT-IR (KBr): ν_{max} (cm^{-1}) 3555 (m), 3445 (m), 3084 (m), 3060 (s), 3026 (s), 3002 (m), 2934 (s), 2836 (m), 2629 (w), 2343 (w), 2047 (w), 1946 (w), 1807 (w), 1661 (w), 1600 (s), 1587 (s), 1492 (s), 1451 (s), 1439 (s), 1389 (m), 1287 (s), 1239 (s), 1181 (m), 1114 (m), 1081 (s), 1030 (s), 936 (w), 878 (w), 846 (w), 825 (w), 780 (m), 753 (s), 700 (s), 623 (m), 601 (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.66 (d, J=6.6 Hz, 1H), 3.71 (s, 3H), 4.42 (d, J=8.2 Hz, 1H), 5.66 (dd, J=8.0, 6.8 Hz, 1H), 6.76–6.81 (m, 2H), 7.07 (m, 2H), 7.11–7.16 (m, 5H), 7.21–7.24 (m, 1H), 7.30 (t, J=7.8 Hz, 2H), 7.35 (d, J=7.3 Hz, 2H); ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ 55.2 (CH_3), 58.2 (CH), 72.8 (CH), 110.4 (CH), 120.5 (CH), 126.1 (CH), 126.5 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 129.2 (CH), 130.4 (C), 141.4 (C), 142.3 (C), 156.5 (C); GC–MS: t_R=35.30 min (*rac*-**21**), m/z (%)=286 ($[M-18]^+$, 20), 271 ($[M-33]^+$, 2), 253 (3), 239 (3), 225 (1), 191 (2), 167 (37), 152 (10), 137 (100), 121 (9), 107 (22), 91 (9), 77 (10); HRMS (ESI^+): calcd for $C_{21}H_{20}O_2Na$ ($[M+Na]^+$) 327.1361, found 327.1349.

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Supplementary data

The NMR spectra of all synthesized compounds, the HPLC chromatograms of **8a** and **9a** as well as semiemprical PM3 geometry optimized structures and Mulliken Population Analysis of the aggregate **II** and **IIIa**. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.05.116.

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